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## STD vaccines—an overview

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**Objectives:** To describe the role and current status of vaccine research against sexually transmitted diseases (STDs).

**Methods:** The available literature was reviewed with particular emphasis on bacterial STDs.

**Results:** Strategic approaches to possible implementation of STD vaccine programmes were analysed. The status of vaccines against bacterial STDs (syphilis, chancroid, gonorrhoea, and chlamydia) is described in detail.

**Conclusions:** The development of safe and effective STD vaccines offers a potent tool for the control of STDs, including direct and indirect prevention of HIV infection. Future priorities should be in the development of vaccines against gonorrhoea, chlamydia, and syphilis. When such vaccines become available, caution should be exercised to ensure that they do not interfere with the effectiveness of other prevention programmes.

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Sexually transmitted diseases (STDs) are a major public health problem in both developed and developing countries. Worldwide it is estimated that over 250 million cases of STDs occur annually, and prevalence rates appear to be far higher in developing countries where STD treatment is less accessible. In many developing countries STDs rank among the top five conditions for which adults seek health care.<sup>1</sup> Today, there are over 20 pathogens classified as sexually transmitted. Over the past 20 years the focus has broadened beyond the traditional "venereal" diseases of gonorrhoea, syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale. Concerns today include bacterial and viral syndromes associated with *Chlamydia trachomatis*, herpes simplex virus (HSV), and human papilloma virus (HPV).

Complications of STDs lead to increased morbidity and mortality in exposed adults and children. Gonorrhoea and chlamydia are the main causes of salpingitis, ectopic pregnancy, and infertility worldwide. Without preventive therapy up to 50% of babies exposed to *Neisseria gonorrhoeae* during birth develop ophthalmia neonatorum.<sup>2</sup> In two thirds or more of pregnant women with syphilis, transplacental spread leads to severe outcomes such as spontaneous abortion, stillbirth, or perinatal death.<sup>2</sup> Congenital syphilis is still an important problem in many parts of the world. HPV infection has been strongly associated with an increased risk of cervical cancer in women.<sup>3</sup> If transmitted to the neonate at the time of vaginal birth, HPV can also cause neonatal and juvenile respiratory papillomatosis.<sup>3</sup>

The preoccupation with STDs became even greater in the 1980s with the advent of the acquired immunodeficiency syndrome (AIDS) caused by the human immunodeficiency virus (HIV). In addition, antimicrobial resistance is a major problem in infections with *Neisseria gonorrhoeae* and *Haemophilus ducreyi*, making some cheap and accessible treatment regimens

ineffective, and thereby favouring the spread of these infections.<sup>4</sup>

Furthermore, there is strong evidence that STDs (both ulcerative and non-ulcerative) are significant contributors to the spread of HIV. Genital ulcer disease (caused by *H ducreyi*, *Treponema pallidum*, and HSV) is recognised as an important cofactor for HIV transmission by providing a more accessible portal of entry (or exit) on contact with genital secretions infected with HIV.<sup>4</sup> In addition, the inflammatory response associated with genital ulceration may increase the number of activated T lymphocytes at the mucocutaneous entry site.<sup>5</sup> Gonorrhoea and chlamydia infections, as well as trichomoniasis, are also implicated in HIV transmission probably due to micro-ulceration and increased local accumulation of activated lymphocytes and macrophages, with a corresponding increase in release of HIV into genital secretions.<sup>4</sup>

Efforts for STD control worldwide, including means for early disease detection, the use of new antibiotics, and emphasis on behavioural intervention such as condom use, have not been totally successful. The World Health Organisation has concluded that the development of effective programmes for the control of STDs is a potential strategy for HIV control.

Immunisation of populations at risk is, in general, a highly effective method of controlling infectious diseases. Vaccines against STDs would provide an important addition to existing prevention technologies for STDs and HIV. Such vaccines have attracted increasing attention as they would offer long lasting and efficient solutions for such important and expensive public health problems.

Apart from the presence of abrasions in/on the reproductive organs or the rectum, agents causing STDs are most likely to infect via the mucosa in the majority of exposed people. It therefore seems logical to develop vaccines that are designed to be administered via the

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mucosa or to stimulate mucosal immunity to prevent or combat these infections.<sup>6</sup> Although a range of information about mucosal immunity and the most effective ways to induce it have been described,<sup>6-8</sup> most of this knowledge concerns the gut. Relatively little is known about mucosal immunity of the genitourinary tract. In developing a vaccine against an infectious agent, there are important factors which must be considered when determining the feasibility of such a vaccine, as previously described.<sup>6</sup>

Among these factors are: (1) the nature of the organism (its complexity), (2) the nature of the infection (acute or chronic), (3) the host's ability to develop natural immunity after infection, (4) whether the organism is cultivatable, (5) the degree of antigenic diversity, and (6) the availability of a suitable animal model.<sup>6,9</sup> In analysing these factors, it would appear that most STD pathogens are structurally complex and confer limited, if any, immunity following infection. Many of these pathogens show significant antigenic diversity, which enables the pathogen to avoid the host's immune system, and may be a major obstacle in vaccine development. Because humans are the only natural host for most STD pathogens, it has been difficult to find an animal model that adequately imitates all aspects of the human disease. However, except for *T pallidum* and HPV, all STD pathogens are cultivatable, which gives us a reason for hope in the challenging task of developing STD vaccines.

### Potential vaccination strategies

A successful vaccination programme may be defined as one that achieves its goal in terms of disease control. For this, the goal must be clearly defined in relation to the disease in question. Likely options are eradication, elimination, or containment.<sup>9,10</sup> Eradication is the permanent and complete removal of the disease and the pathogen. Elimination is the disappearance of the disease with the causal agent remaining, either in non-human hosts, or as subclinical infection in humans. Containment is the control of the disease to the point at which, although not eradicated, it no longer constitutes a public health problem.<sup>6,9,11</sup> Important factors for successful immunisation programmes are vaccine safety as well as efficacy and characteristics of the infection. An infection with potential to be eradicated includes the absence of a non-human host, easily identifiable clinical manifestations, the absence of subclinical or latent infection, low infectivity, and lifelong immunity following vaccination<sup>9,10,12</sup> (in the case of STDs it would only be necessary during sexually active years). The fact that the classic STD agents are pathogenic only in humans favours their eradication. However, the tendency of certain STD pathogens (gonococcus, chlamydia, HSV) to cause subclinical or asymptomatic infection in some individuals indicates that these organisms can effectively avoid the host immune system.

For successful implementation of any vaccination strategy the target population must be

carefully defined and its easy accessibility assured. Previous immunisation programmes carried out by the WHO showed us that the effectiveness of any immunisation strategy will always depend on the ability to access reliably and consistently the populations targeted for vaccination, and on the ability to provide reliably and consistently a potent vaccine to such populations. As one can expect, different STDs may require different vaccine strategies. If the aim is eradication or elimination, universal vaccination is required (with a vaccine that provides lifelong immunity), which is usually accomplished during infancy or childhood. However, this is an expensive strategy and might not be widely accepted. Containment could conceivably be accomplished by selective immunisation of those at highest risk of acquiring STDs or transmitting them to others (for example, adults in sexually active years). An alternative strategy would be to develop a vaccine that would be effective in only males or females.

Immunisation of one would probably, as a result, prevent infection in the other. A disadvantage of selective vaccination is that it is often difficult to identify or access groups most at risk and ensure adequate coverage of vaccine. However, a selective STD vaccination strategy could mimic considered strategies for HIV vaccine in developing countries. These strategies include targeting urban adolescents and young adults (10–19 years old) attending school, and women of childbearing age accessed by EPI (WHO Expanded Program on Immunisation) to receive the tetanus toxoid.<sup>13</sup> A strategy to accomplish maximum coverage should focus at two different goals: (1) containment, by targeting adults in the sexually active period (most likely 15–49 years old, with priority to 15–25 years of age) to ensure rapid “mopping up” of those people at risk of infection; while (2) aiming at elimination by ensuring integration of vaccination into existing programmes, such as EPI, and school immunisation programmes to replace the “mopping up strategy” once those immunised at young ages reach sexual activity.

The objective of an STD prevention strategy through vaccination is STD prevention and control and prevention of HIV infection. Therefore, it is crucial that other STD control and HIV prevention interventions be maintained, even as HIV and STD vaccine delivery to populations are implemented. Any STD vaccination programme must be linked to more effective counselling. Prevention of classic STDs does not prevent the need for behavioural changes to reduce the risk of HIV transmission.

Next, we briefly review the current state of research for development of vaccines for bacterial STDs.

### Syphilis

Despite numerous attempts, continuous in vitro cultivation of *Treponema pallidum* subsp. *pallidum* (TPP) has not yet been accomplished, although limited propagation and

single passage survival have been achieved in a tissue culture system.<sup>14</sup> Therefore, current knowledge of TPP metabolism, physiology, and antigenic structure has been derived from organisms propagated by passage in experimental animals, usually rabbits. It is well known that some level of acquired immunity develops during the course of both human and experimental syphilis. Approximately one third of infected individuals are able to cure their infection and have no residual antibody to *T pallidum*; one third develop latent syphilis with no clinical signs or symptoms but with lifelong seropositivity; and the rest progress to tertiary syphilis. In the study at Sing Sing Prison, conducted nearly 40 years ago, Magnuson *et al* injected live *T pallidum* into the skin of adult male prisoners and looked for development of lesions with spirochaetes visible by dark field microscopy. Subjects with no previous history of syphilis developed lesions, whereas individuals with untreated latent syphilis (who therefore had serum antibody titres) were relatively protected. In fact, 13 of 26 patients with previously treated late latent syphilis and all five patients with untreated late latent syphilis did not develop clinical manifestations at the site of challenge. All patients (11 of 11) with treated primary or secondary syphilis developed skin lesions at the site of inoculation.<sup>15</sup> These results indicate that existence of slowly developed immunity. These findings were confirmed in rabbit or hamster models: complete resistance to exogenous challenge develops only after 3–6 months of infection, well after the healing of the early lesions.<sup>16</sup>

There is now convincing evidence that T cell mediated delayed type hypersensitivity (DTH) is the predominant immune mechanism for clearing tissues of infecting organisms in the primary lesion of syphilis. Effective immunity to syphilis is mediated by T cells secreting lymphokines which activate macrophages to destroy infecting organisms; antibody and cytotoxic T cells (CTL) have little effect on *T pallidum* in tissues.<sup>17</sup> It is postulated that cure of syphilis is caused by strong DTH, latency being caused by intermediate strength DTH, and tertiary disease by weak DTH with relatively strong antibody formation. Application of this hypothesis to development of a vaccine strategy against syphilis indicates that a vaccine should induce DTH, rather than antibodies or CTL. Previous attempts to develop syphilis immunity using avirulent treponemes, attenuated or heat inactivated organisms, as well as extracts of pathogenic organisms have been partially successful in a few cases. Miller<sup>18</sup> achieved complete long term protection (1 year) following a 37 week, 60 intravenous injection, immunisation schedule using large doses of gamma irradiated organisms. Sell and Hsu reported protection using a large number of organisms and lengthy inoculation protocols.<sup>17</sup> All these protocols are impractical for common experimental or clinical applications. In addition, most of the vaccination strategies used in the past have focused on production of circulating antibody (antigen

presentation by follicular dendritic cells), not sensitised T cells.<sup>17</sup> Lately, with the availability of cloned *T pallidum* genes a number of new approaches have become feasible for the development of effective vaccines, including: (a) purified recombinant antigens, (b) synthetic peptide antigens, or (c) vectored vaccines. The protein Tpn19, partially protected rabbits against intradermal challenge with *T pallidum*, as well as recombinant endoflagellar protein and another antigen, Tpn36 (also known as TmpB), which also partially protected animals against infection.<sup>9</sup> Recent experiments have directed attention towards vectored vaccines. In order to induce DTH, the antigen needs to be presented by the exogenous rather than the endogenous pathway.

It now appears that BCG (Bacille-Calmette-Guerin) a live, attenuated bovine tubercle bacillus, widely used to immunise against tuberculosis) might be the ideal vaccine vector for *T pallidum* antigens. It is believed that BCG may provide a vector for the *T pallidum* antigens that has the potential to induce a high level of DTH.<sup>17</sup> BCG vectored vaccination against *T pallidum* antigens is advocated as a feasible, inexpensive, and as a strong candidate for effective vaccination against human syphilis<sup>17</sup> by specific induction of DTH.

### Chancroid

Although *H ducreyi* was first described in 1889,<sup>19</sup> little is known about its essential virulence factors or about the pathogenesis of chancroid. The organism's ability to cause ulcers on stratified squamous epithelium suggests that *H ducreyi* produces cytotoxins or other extracellular products capable of destroying tissues.<sup>4</sup> Recent data indicate that most strains of *H ducreyi* have the ability to produce a cytotoxin with high cytotoxic activity specific to human cell lines.<sup>19</sup> Cytotoxin produced by *H ducreyi* caused death of epithelial cells grown in cell culture. The cytotoxic activity was neutralised by homologous rabbit immune serum.<sup>19</sup> Intradermal inoculation of rabbits with *H ducreyi* cytotoxin preparations induced toxin neutralising antibodies that cross reacted with heterologous cytotoxin producing strains. Preparations with non-cytotoxin producing strains of *H ducreyi* or other Gram negative bacteria did not induce toxin neutralising antibodies.<sup>20</sup> Nevertheless, natural infection of humans leads to the production of antitoxin antibodies, although without evident protection from disease.<sup>20</sup> The actual role of the cytotoxins in the pathogenesis of human chancroid remains unclear, with much still to be accomplished in the understanding the genetics, biochemistry, and immunobiology of the putative toxin(s). The great interest in the cytotoxin(s) is due to the fact that many other cytotoxins can be used to create effective vaccines, including diphtheria toxin.<sup>4</sup>

A number of other *H ducreyi* proteins have also been identified, including outer membrane proteins and pili.<sup>4</sup> Some of these proteins present antigenic variations during

infection of a subcutaneous chamber, a mechanism to avoid host defence that could explain the ability of *H ducreyi* to persist in vivo.<sup>4,21</sup> The immune response to human chancroid is not yet understood, but there is evidence for both T cell<sup>4</sup> and B cell response. It is not likely that an effective vaccine against *H ducreyi* will be developed in the near future, but progress has been made in developing models to study the pathogenesis of *H ducreyi* infection. Recent studies have developed a safe and reproducible human experimental model of *H ducreyi* infection.<sup>9</sup> Application of live *H ducreyi* to abraded skin resulted in papule and pustule formation. This model should facilitate study of the human response to *H ducreyi*.

### Gonorrhoea

Gonococci are limited to a human host and most commonly result in symptomatic or asymptomatic colonisation of one or more mucosal surfaces.<sup>22</sup> Attempts to generate a gonococcal vaccine have been limited by various factors. There is no simple, credible animal model of mucosal disease. In addition, there is little recognition and understanding of phenotypic variation in vivo, and little understanding of the mucosal response to gonococcal infection and its significance.<sup>22</sup>

The interaction of gonococci with human cells is mediated mainly by components of the outer membrane, and any protective immune response is also likely to be primarily directed against these components. The outer membrane of the gonococcus is typical of most other Gram negative bacteria and contains multiple proteins and lipo-oligosaccharide (LOS). Virtually all Gram negative bacteria contain porins that form channels through the lipid rich outer membrane. To date, only one porin has been identified in the gonococcus, and it is termed "protein I" (PI) or "Por".<sup>23</sup> Two subgroups of Por exist—A and B.<sup>9,23</sup> Protein I appears to be important in serum resistance, antimicrobial susceptibility, and invasiveness.<sup>23</sup> PIII is another outer membrane protein found on all gonococcal isolates. It is important because it is very immunogenic in humans and because antibody to PIII may block the killing effects of otherwise bactericidal antibodies.<sup>23</sup> Opa (formerly called protein II) consists of a group of outer membrane proteins that share the phenomenon of heat modifiability. Opa protein increases adherence between gonococci, increases attachment of gonococci to other cells, and causes colony opacity.<sup>9</sup> The importance of the Opa family in the pathogenesis of the gonococcus is based on their ability to mediate adherence to several different eukaryotic cells. Marked phase and antigenic variation of Opa appears to limit its use as a vaccine. Pili (or fimbriae) are surface organelles that have been studied intensively because of their role in pathogenesis and their possible use in vaccines. Only piliated gonococci are virulent in human challenge studies, probably because pili are important to the initial adherence to epithelial cells.<sup>23</sup> For this reason pilus vaccines have received the most attention.

### Pili as vaccine candidates

Many studies demonstrate that antisera produced in laboratory animals by immunising with purified or partially purified pili have a protective effect in a variety of biological systems. Anti-pilus antisera reduce the adhesion of both piliated gonococci and purified pili to epithelial cells, opsonise gonococci for phagocytosis by polymorphonuclear leucocytes, and protect tissue cultured cells from the cytotoxic effect of challenge with gonococci.<sup>24</sup> Human volunteers immunised with pili produce detectable anti-pilus antibodies in both serum and genital secretions, which are also able to inhibit cell attachment.<sup>25</sup> Although studies using human volunteers indicate a protective effect, in most studies the test was performed using homologous strains. Therefore, concerns of the use of pili for vaccination are raised because of their extreme antigenic and structural diversity.<sup>24</sup> Although sera from immunised volunteers inhibited attachment of heterologous strains to cells in vitro, the vaccine did not protect against infection when volunteers were challenged with heterologous strains.<sup>9,24</sup> Despite structural homology pili from different strains are antigenically distinct.<sup>24</sup> Owing to this remarkable antigenic heterogeneity and the lack of protection observed against heterologous infection the use of pilin vaccines is not anticipated unless extreme antigenic conservation<sup>9,24</sup> can be demonstrated.

### Other possible vaccine candidates

Other gonococcal proteins might act as candidates for vaccines. Attention has been driven to Por vaccines. Por, the major outer membrane protein, is stably expressed (does not present antigenic variation and/or mimicry to host's antigens like other gonococcal surface components) and occurs in a relatively small number of serovars or serogroups (A and B).<sup>23</sup> This makes Por (PI) an attractive candidate for gonorrhoea vaccine. Infection with one type of Por serovar may decrease the likelihood of recurrent infection with a strain with the same type of porin protein. However, the presence of serum antibodies to Por does not protect against infection.<sup>9</sup> Rabbit antisera against Por A and Por B peptides demonstrated bactericidal activity for homologous gonococcus and many heterologous serovars.<sup>9</sup> There is evidence that a host response to PI is important to gonococcal infection.<sup>9,26</sup> In a study of repeat gonorrhoea infection of prostitutes in Kenya, Plummer *et al*<sup>27</sup> found a significant decrease in the risk of reinfection with a strain of the same PI serovar. However, since reinfection did occur, neutralising antibodies were probably raised only to type specific and not common epitopes on PI. An effective immune response to PI may be hindered by blocking antibodies directed against protein m (Pm or Rmp),<sup>28</sup> another abundant surface antigen which is closely associated with PI in the outer membrane. PI preparations from gonococci inevitably contain significant levels of contaminating PIII. The blocking antigen effect of PIII was also observed in a vaccine study using Por as the immunogen.<sup>29</sup> Although

the vaccine induced a significant antibody response it did not protect men from challenge with the homologous gonococcal strain. It was suspected that the vaccine was contaminated with blocking antigen (Rmp) that interfered with vaccine efficacy. A laboratory constructed PII deficient gonococcal strain (purified Por) may permit immunisation without the problem of generating blocking antibody. When formulated into a liposome preparation and administered to rabbits purified Por elicited bactericidal and opsonic antibodies.<sup>9</sup> Monoclonal antibodies to PI raised in the laboratory have been shown to be broadly cross reactive against many different gonococcal strains within a PI serotype, and to have a bactericidal, opsonic, and protective effect against cell invasion and damage.<sup>26</sup> These are desirable immunological properties for a vaccine candidate. However, sialylation of lipo-oligosaccharide (LOS) may inhibit the function of a Por vaccine. LOS lies in proximity to Por in the outer membrane. Sialylation of LOS abolished the bactericidal effect of antisera to Por peptides by partially blocking surface exposure of Por epitopes and also by inhibiting complement activation.<sup>4,9</sup> Nevertheless, the blocking effect of sialylation is incomplete and could be overcome.<sup>9</sup> The recently constructed strains of recombinant *Salmonella typhimurium* that expressed gonococcal Por<sup>4</sup> may permit investigation of the potential of an oral vaccine using *S typhimurium* expressing Por. This approach would stimulate both humoral and mucosal immunity, which are essential for an effective gonococcal vaccine.

LOS is another potential vaccine candidate. Unfortunately, gonococcus has developed several mechanisms to evade attack by this potential immunogen. (1) LOS core sugars mimic some host antigens reducing the immune response. (2) Phase and antigenic variations result in altered length and composition of core sugars and loss of terminal epitopes, with a frequency similar to Pil and Opal. (3) Sialylation of the terminal core sugars in vitro and in vivo, lessens bactericidal activities of serum antibodies. This process inhibits complement deposition and antibody attack on both LOS and Por.<sup>4</sup>

Attention has also been given to the outer membrane receptors that bind host iron, such as transferrin (Tbp1, Tbp2) and lactoferrin (Lbp1, Lbp2) which remove iron from transferrin, as possible candidates for a gonococcal vaccine.<sup>4,9</sup> Gonococci require iron for growth and produce several iron regulated proteins in response to iron depleted environments which function in the acquisition of iron from the human host. Comparisons of the predicted protein sequences for Tbp1 and Tbp2 appear to be similar for gonococcus and meningococci.<sup>4,9,23</sup> Antibodies against meningococcal Tbp1 and Tbp2 block meningococcal transferrin binding, cross react rather broadly among meningococci, and are bactericidal.<sup>4,9,23</sup> These proteins may play a role in gonococcal pathogenicity. Antibodies to them are produced in response to infection.<sup>23</sup> Studies have still to be conducted with gonococcal Tbp1 and Tbp2, but the limited data available are promising.

Considering the study results of Por, Pil, Opa, and LOS, an ultimate vaccine candidate for gonococcus might be one that does not suffer high frequency antigenic variations, that is not protected by anti-Rmp blocking antibodies, and that is not masked by sialylation. It should also contain one or a few epitopes that are conserved and that are targets for protective antibodies. Por remains the most attractive candidate owing to its relatively limited antigenic variation and weak epidemiological evidence that this protein may provide partial Por based immunity.

### Chlamydia

Chlamydiae, like viruses, have an obligate intracellular existence. There are 15 principal serovars arranged into three serogroups. Serovars A, B, and C cause endemic trachoma, while serovars D to K are responsible for a variety of genital tract diseases (urethritis, cervicitis, salpingitis).<sup>4,30</sup> The pathology due to chlamydial infections appears to be immunologically mediated, and hypersensitivity may contribute to the disease.<sup>30</sup> Hypersensitivity has accounted for the relatively unsuccessful attempts to vaccinate against trachoma. In previous studies, vaccination with killed chlamydia frequently resulted in more severe trachoma after reinfection.<sup>9</sup> Ocular scarring and blindness result from chronic and repeated infection. Serovar specific immunity develops over time, but other serovars remain infectious and trigger an apparent hypersensitivity response.<sup>4</sup> A chlamydial 57 kD heat shock protein elicits a delayed hypersensitivity response in immune animals with resultant ocular inflammation.<sup>9</sup> The inflammatory response to the 57 kD protein may contribute to complications of infections and to the development of chronic inflammatory sequelae that follow *C trachomatis* infection in humans.<sup>4,9</sup>

Studies have shown that, among infected women, the presence of antibodies to this protein is associated with increased risk of salpingitis, ectopic pregnancy, and tubal infertility.<sup>4,9,31</sup> None the less, other chlamydial antigens may induce a protective immune response. The best evidence for a protective role involves the major outer membrane protein (MOMP). MOMP is the primary chlamydial serotyping antigen whose determinants form the basis for serological classification of *C trachomatis* isolates. It is surface exposed, is highly immunogenic, and is a major target for neutralising antibodies.<sup>32</sup> MOMP is the only surface component for which neutralising antibodies have been identified.<sup>9</sup> Antibodies against MOMP are neutralising and protective against chlamydial infectivity for culture eukaryotic cells and against toxic death in mice after chlamydial challenge.<sup>4,9,32</sup> This supports the notion that MOMP is a major protective antigen and a primary target antigen for chlamydial vaccine development.

Some MOMP antibodies neutralise multiple serovars.<sup>4,9</sup> Protection may be expanded to subspecies specific epitopes although not to all serogroups of chlamydiae.<sup>4</sup> The cloning and sequencing of MOMP genes lead to the identifi-

cation of four variable domains (VD I-IV) whose sequences vary among the different serovars.<sup>4,9,32</sup> These variable domains may be important in binding of the organisms to host cells. Antibodies specific to MOMP VD epitopes are neutralising and prevent infectivity by blocking chlamydial adherence to host epithelial cells.<sup>32</sup> An epitope composed of a seven amino acid sequence of MOMP VDIV is highly conserved among most *C trachomatis* serovars and elicits a neutralising monoclonal antibody.<sup>4,9</sup> This peptide was coupled to a T helper cell epitope (A8) to increase the immunogenicity of neutralising B cell epitopes and to provoke chlamydial specific T cell memory. The resultant peptide was immunogenic in mice and monkeys and neutralised *C trachomatis* infectivity in vitro.<sup>4,9,32</sup> The vaccine did not protect monkeys from challenge with *C trachomatis*, however, probably because of the inability of serum IgG antibodies to translocate to epithelial cells and localise at mucosal surfaces.<sup>9</sup> Nevertheless, these results suggest that a synthetic peptide vaccine against genital chlamydia is possible, although it is necessary to use strategies to evoke a secretory neutralising antibody response. Similarly, a peptide of a T helper epitope and VDI brings enthusiasm towards a trachoma vaccine.<sup>4</sup> Another approach is the use of recombinant MOMP (rMOMP) itself. Rabbits challenged with rMOMP developed an antibody response almost entirely directed against the variable, surface exposed, neutralising regions on MOMP.<sup>33</sup>

Ideally, a chlamydial vaccine should induce neutralising mucosal antibody. In practice, mucosal immunity is difficult to sustain in the absence of replicating antigen. Recent studies show that guinea pigs infected intestinally with *C psittaci* are protected from challenge at both conjunctival and vaginal mucosae.<sup>32</sup> The delivery of MOMP antigens to the intestinal mucosa might be accomplished through oral vaccination with microencapsulated immunogens or with infectious enteric vaccine vectors (for example, attenuated salmonella strains) expressing MOMP immunogens.<sup>30,32</sup> Most likely, in the absence of high concentrations of mucosal antibodies it will be difficult to prevent initial infection of host cells. After vaccination, high level of anti-chlamydia circulating antibody should be achieved easily and, following initial infection, might gain access to the epithelia by inflammatory transudation. Although not preventing initial infection, such antibody might be capable of neutralising released chlamydiae, modifying the severity of disease and decreasing individual infectivity in the community<sup>30</sup> which, therefore, would reduce the high morbidity/sequelae associated with chlamydial infection.

### Conclusion

STDs prevail as an important and costly public health problem worldwide. Owing to the serious morbidity and sequelae, priorities for vaccine development might be towards gonorrhoea, chlamydia, and syphilis. As research continues and much progress has

been made towards vaccine development for most STDs, it is still not predictable when these vaccines will become available. The problem of stimulating long term immunity in the genital tract is still a challenge as little knowledge is available on genital tract immunology. Nevertheless, there are reasons for optimism. Until STD vaccines become available (and even when STD vaccines are delivered to the population), it is very necessary that other STD control and HIV prevention programmes be continued, as immunisation for STDs does not preclude the need for STD screening, treatment, and behavioural changes to reduce the risk of HIV transmission. On the other hand, efforts for vaccine development should remain in place since they are promising solutions for such important public health problems.

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